In the United States Court of Federal Claims

No. 01-565V
(Filed under seal July 8, 2014)
(Reissued July 25, 2014)[†]

[M.S.B.], by her mother and natural guardian, TIFFANY BAST, Petitioner, v. **SECRETARY OF HEALTH AND HUMAN SERVICES,** Respondent.	Vaccine Act off-table petition; IPV, DTaP, Hib, hepatitis B vaccines; seizure disorder; reactive oxygen species; oxidative stress; weight of contemporaneous medical records; mitochondrial disorder; rechallenge; *Althen* prongs; unreliable medical theory; factual predicate not proven; medically-inappropriate time frame.

Clifford J. Shoemaker, Vienna, Virginia, for petitioner.

Ann D. Martin, Senior Trial Attorney, Torts Branch, Civil Division, Department of Justice, with whom were *Stuart F. Delery*, Assistant Attorney General, *Rupa Bhattacharyya*, Director, *Vincent J. Matanoski*, Deputy Director, and *Catharine E. Reeves*, Assistant Director, all of Washington, D.C., for respondent.

OPINION AND ORDER

WOLSKI, Judge.

Petitioner Tiffany Bast has moved for review of then-Chief Special Master Patricia Campbell-Smith's decision that petitioner is not entitled to compensation under the National Vaccine Injury Compensation Program, 42 U.S.C. §§ 300aa-10–

[†] At petitioner's request, her minor daughter's name has been replaced with initials. The opinion is reissued for publication with some minor, non-substantive corrections.

300aa-34 (Vaccine Act or Act).[1] The petition, which was filed by Mrs. Bast on behalf of her daughter, [M.S.B], on October 1, 2001, contended that [M.S.B.] suffered "seizures, encephalopathy, and liver damage" as a result of the hepatitis B vaccine administered on October 23, 1998. Pet. at 1–2. In later filings, it was alleged that the inactivated polio, diphtheria-tetanus-acellular pertussis, Haemophilus influenzae type B, and hepatitis B vaccines that [M.S.B.] received on December 4, 1998, caused her neurodevelopmental disorders and epilepsy. Pet'r's Ex. 51 at 4; Pet'r's Post-Hr'g Br. at 4. Petitioner raised three objections to the Chief Special Master's decision denying compensation, arguing that her decision was arbitrary and capricious and failed to follow the standards of *Althen v. Sec'y of Health & Human Servs.*, 418 F.3d 1274 (Fed. Cir. 2005). Pet'r's Mot. for Rev. at 2. For the reasons stated below, the Court **DENIES** petitioner's motion and **SUSTAINS** the decision of the Chief Special Master.

I. BACKGROUND

A. The Vaccinations and Medical History[2]

[M.S.B.] was born on October 11, 1998, after a complicated pregnancy. Pet'r's Ex. 12 at 35. On March 27, 1998, at the beginning of the second trimester, Mrs. Bast was involved in an automobile accident. Pet'r's Ex. 4 at 2; Pet'r's Ex. 12 at 25. Following this incident, Mrs. Bast suffered from migraine headaches, for which she was prescribed Vicodin. Pet'r's Ex. 4 at 2; Pet'r's Ex. 12 at 25. Petitioner also contracted a respiratory infection during the second trimester, and was given antibiotics and prescription strength Robitussin AC to treat the infection and a cough that she developed. Pet'r's Ex. 4 at 3. In the third trimester, Mrs. Bast fell and tore the round ligament of her uterus. Pet'r's Ex. 19 at 217. She was placed on bed rest and was again prescribed Vicodin. *Id.*

[M.S.B.] was carried to full-term, and weighed eight pounds and thirteen ounces at birth. Pet'r's Ex. 12 at 29. During labor, [M.S.B.]'s umbilical cord became wrapped tightly around her neck and had to be removed at birth. Pet'r's Ex. 13 at 10, 20. When she was delivered, [M.S.B.]'s Apgar scores were 8 and 9, Pet'r's Ex. 12 at 15, and her newborn exam was normal, *see* Pet'r's Ex. 13 at 20. [M.S.B.] was discharged from the hospital the day after she was born. Pet'r's Ex. 12 at 16.

[M.S.B.] received her first hepatitis B vaccine in an office visit with her pediatrician, Dr. Peri Gunay, M.D., twelve days after she was born. *See* Pet'r's Ex.

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[1] The Honorable Patricia Campbell-Smith has since become the Chief Judge of our court. This opinion will refer to her using the position she held when the decision was issued.

[2] The background facts are primarily drawn from the Chief Special Master's opinion, with any relevant disputes concerning these facts specifically noted.

23 at 9. At this visit, Dr. Gunay noted slackness in her right hip, but no "clicks or clunks," as would be indicative of a hip joint problem. *Id.* On November 4, 1998, [M.S.B.] returned to see Dr. Gunay for a sick visit, presenting with slight nasal congestion, occasional vomiting, and mucous that had been draining from her right eye for one day. *Id.* at 6. At this visit, [M.S.B.] did not have a fever, and Dr. Gunay determined that she had conjunctivitis in her right eye. *See id.*

[M.S.B.] returned to Dr. Gunay's office on December 4, 1998, for a well-child visit. Pet'r's Ex. 23 at 9. At this visit [M.S.B.] presented with a mild cold. *See id.* Although flattening of the back of [M.S.B.]'s head was noted during her visit, no concerns about her growth and development were noted. *See id.* [M.S.B.] received the vaccinations that petitioner contends caused [M.S.B.]'s subsequent medical problems during this visit --- specifically, her first inactivated polio (IPV), diphtheria and tetanus toxoid with acellular pertussis (DTaP), and Haemophilus influenzae type B (Hib) vaccines, and her second hepatitis B vaccine. *See id.*

At some point after this visit, [M.S.B.] developed more serious cold symptoms. There is some dispute, however, as to the timing of the onset of these symptoms. [M.S.B.]'s parents filed a joint affidavit contending that [M.S.B.] developed a "pretty bad" upper respiratory infection "within ten days of the vaccine," requiring a visit to the pediatrician. Pet'r's Ex. 25 at 2. Based on this timing, [M.S.B.] would have visited the pediatrician's office on or about December 14, 1998. However, a review of [M.S.B.]'s contemporaneous medical records indicates that [M.S.B.] did not return to the pediatrician's office until December 30, 1998, at which time she presented with cold symptoms that were noted as having been present for one week. Pet'r's Ex. 23 at 6.

There is also some dispute as to the timing of [M.S.B.]'s first seizures. [M.S.B.]'s medical records reflect that on January 11, 1999, Mrs. Bast called the pediatrician's office to report that [M.S.B.] had "three brief spells involving stiffening, eye deviation [and] rhythmic movements of extrem[ities]," each of which lasted a few seconds. Pet'r's Ex. 23 at 6. Doctor Gunay indicated that [M.S.B.] was to be seen "ASAP," and he examined [M.S.B.] later that day. *Id.* The notes from Dr. Gunay's examination indicate episodes of "seizures" that involved an "altered mental status," "eye deviations," and "twitching movements" over the "past five days." *Id.* But in their affidavits, [M.S.B.]'s parents recalled that [M.S.B.] began to have "little" tics roughly one week after her upper respiratory infection and the associated trip to the pediatrician, which was "less than three weeks after her immunizations." Pet'r's Ex. 25 at 2. This would date the onset of these symptoms on or about December 21, 1998. The Basts further declared that these tics turned into grand mal seizures "[b]y January 4, 1999." *Id.*[3]

[3] The Chief Special Master accorded more weight to the contemporaneous medical records, citing the diligence of [M.S.B.]'s parents in seeking treatment and the

At the January 11 visit, Dr. Gunay made note of [M.S.B.]'s recent upper respiratory infection, in which she had nasal congestion and cough, but no fever. Pet'r's Ex. 23 at 6. He also consulted with Dr. Stuart Stein, M.D., a pediatric neurologist, and concluded that [M.S.B.] should start anti-seizure medication only if the frequency of her seizures increased. *See* Pet'r's Ex. 19 at 216. [M.S.B.]'s seizure activity increased the next day to about four or five, typically occurring after she was fed. *Id.* Doctor Gunay examined [M.S.B.] again on January 13, 1999, and started [M.S.B.] on the anticonvulsant. *Id.* At this visit, Dr. Gunay also ordered an electroencephalogram (EEG) for [M.S.B.]. *Id.* at 210. The EEG was performed the following day, and the results were "markedly abnormal" due to "very active epileptiform potentials . . . in the right frontal central area." Pet'r's Ex. 1 at 165.

Doctor Stein examined [M.S.B.] on January 15, 1999, noting that she appeared to have a seizure disorder. Pet'r's Ex. 19 at 214. [M.S.B.] exhibited signs of weakness and diminished muscle tone, Pet'r's Ex. 15 at 93, and Dr. Stein indicated that she may have a "possible metabolic disorder" or a "possible post infectious encephalopathy," Pet'r's Ex. 19 at 214. While at Dr. Stein's office, [M.S.B.] had two or three seizure episodes of greater duration than usual. *See id.* at 214; Pet'r's Ex. 15 at 93. Doctor Stein recommended that [M.S.B.] be admitted to the hospital for treatment and that she receive a computed tomography (CT) scan in order to begin to rule out some of the possible causes of her seizures --- in particular, factors such as a brain abnormality, a metabolic disorder, an infectious process, Guillain-Barré, or demyelinating diseases. *See* Pet'r's Ex. 19 at 218.

[M.S.B.] was admitted to the hospital where she was started on the anticonvulsant Dilantin. *See* Pet'r's Ex. 23 at 166. The results of [M.S.B.]'s CT scan and testing of her cerebrospinal fluid ruled out a post-infectious encephalopathy, but indicated possible abnormalities in her brain formation. *See* Pet'r's Ex. 1 at 162. Based on [M.S.B.]'s lab results, which indicated insufficient carnitine, Dr. Stein questioned whether [M.S.B.] had an energy metabolic disorder. *See* Pet'r's Ex. 23 at 167. [M.S.B.] also exhibited symptoms of "Todd's paralysis" while in the hospital --- a condition marked by temporary paralysis following seizures. *See id.* at 162, 166.

Before being discharged from the hospital on January 17, 1999, [M.S.B.] was diagnosed with a seizure disorder and an absent corpus callosum. *See* Pet'r's Ex. 19 at 212. She continued to take both Dilantin and Phenobarbital upon release from the hospital in an attempt to control her seizures. *See* Pet'r's Ex. 23 at 162. Doctor Stein evaluated [M.S.B.] a few days later, and noted that at that time, he thought

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thorough documentation of her medical appointments. *See Bast ex rel. Bast v. Sec'y of Health & Human Servs.*, No. 01-565V, 2012 WL 6858040, at *8–9 (Fed. Cl. Sp. Mstr. Dec. 20, 2012).

she had "an idiopathic seizure disorder," but that the possibility that she had "a disorder of energy metabolism" should also be considered. *See* Pet'r's Ex. 23 at 167. He started [M.S.B.] on a carnitine treatment to address the possible energy metabolism disorder, but [M.S.B.]'s seizure activity did not decrease in response to this treatment --- instead increasing to about twenty to thirty seizures per day. *See* Pet'r's Ex. 23 at 162–63, 168.

On January 29, 1999, [M.S.B.] was hospitalized again, this time for two days. *See* Pet'r's Ex. 11 at 90, 98. While at the hospital, a magnetic resonance imaging (MRI) scan was taken of [M.S.B.]'s brain, and the results showed a brain abnormality --- "[f]ocal thickening and irregularity of the right frontal lobe gray matter" --- which suggested a "focal migrational anomaly." *See* Pet'r's Ex. 1 at 141–42. This type of anomaly is a birth defect caused by the abnormal migration of neurons during brain and nervous system development. *See Bast*, 2012 WL 6858040, at *18. The MRI report also indicated that [M.S.B.] had a "[t]iny left frontal lobe subdural hematoma," *see* Pet'r's Ex. 1 at 142, which may have been caused by her vacuum extraction at birth, Pet'r's Ex. 11 at 97.

On February 5, 1999, [M.S.B.] was examined by Dr. Raman Sanker, M.D., another pediatric neurologist. Pet'r's Ex. 23 at 162–63. At this visit, Dr. Sanker noted that [M.S.B.]'s head circumference was forty-one centimeters, which put her in the fiftieth percentile for her age, and that her "fontanelle anteriorly is soft and open." *Id.* at 163. He also noted that [M.S.B.] had a right gaze preference and preferred to lie to the right side, and that her face appeared to be intermittently weak on the left side. *Id.* Another EEG was ordered that month, and the results were markedly abnormal. *Id.* at 163–64.

[M.S.B.] was referred to the Advanced Epilepsy Management Clinic at the University of California, Irvine, where on February 15, 1999, she was seen by Dr. Tallie Baram, M.D., a pediatric neurologist. *See* Pet'r's Ex. 1 at 168; Pet'r's Ex. 23 at 159. After another EEG, which showed a "very irritative encephalopathy," Dr. Baram concluded that [M.S.B.] had an "abnormal brain, likely a [neuronal] migration abnormality, associated with a multifocal, irritative cortex" and identified her condition as severe multifocal epilepsy. *See* Pet'r's Ex. 23 at 160. Doctor Baram also noted that [M.S.B.] had infantile spasms, and recommended that she be treated for the spasms before addressing their source. *See id.* Doctor Baram recommended that [M.S.B.] be given adrenocorticotropic hormone (ACTH) for her infantile spasms, and that her other medications be limited to phenobarbital and pyridoxine, a form of vitamin B6. *See id.* at 160–61.

Shortly thereafter, [M.S.B.] was examined by Dr. Keith DeOrio, M.D., a family physician who offers alternative healing therapies. *See* Pet'r's Ex. 36 at 2. As of that time, Dr. DeOrio noted that [M.S.B.] was taking phenobarbital, had elevated liver enzymes, and was having approximately fifty-five seizures per day.

Id. On March 1, 1999, [M.S.B.] had a follow-up appointment with Dr. Baram, who again recommended ACTH, noting that based on her prior evaluation of [M.S.B.], it did not appear that she had "a mitochondrial disorder or any other disorders which would preclude her from starting on ACTH." *See* Pet'r's Ex. 23 at 157.

At a follow-up appointment approximately three weeks later, on March 22, 1999, Dr. Baram noted that [M.S.B.] had "responded beautifully" to a "two-week dose of ACTH, at a high dose." *See id.* at 155. Doctor Baram indicated that [M.S.B.]'s infantile spasms were gone, that her EEG testing had improved, and that [M.S.B.] showed improvements in alertness and her ability to visually track and hear. *See id.* [M.S.B.] was experiencing an emerging focal seizure disorder, which Dr. Baram indicated would be treated with topiramate. *Id.* [M.S.B.] also underwent testing for any infection process and the results were negative. *See* Pet'r's Ex. 1 at 121–25.

[M.S.B.]'s medical records indicate that she was tested for a variety of conditions beginning in July of 1999. Doctor Stein examined [M.S.B.] on July 2 and indicated that he was unsure whether [M.S.B.] had a metabolic disorder or whether she was acidotic as a result of her frequent seizures. *See* Pet'r's Ex. 1 at 105. Doctor Stein ordered metabolic testing, and the results of the tests were normal, except for high levels of lactic acid in her urine. *See id.* at 95. In August of 1999, Dr. Sidney Gospe, M.D., another pediatric neurologist, conducted additional testing and concluded that [M.S.B.] did not have pyridoxine-dependent seizures. *Id.* at 54–55. Instead, he attributed the seizures to "a developmental brain anomaly," and recommended another MRI to examine this possibility. *Id.* at 55. Doctor Gospe also recommended that [M.S.B.] continue to receive all regular vaccinations, indicating that her prior evaluations failed to reveal any specific metabolic abnormalities and that he did not believe that her epileptic encephalopathy was related to her previous hepatitis immunization. *Id.* He did, however, note that [M.S.B.] showed evidence of precocious puberty --- namely, bilateral breast development --- which may be attributable to "exogenous estrogen ingestion" or medication that she had taken. *Id.*

A brain scan in September of 1999 showed a mild decrease in the maturation of [M.S.B.]'s brain's white matter and a delay in the maturation of her corpus callosum, indicating abnormal brain development. *See* Pet'r's Ex. 1 at 43–44. The issue of whether [M.S.B.] had a mitochondrial disorder was evaluated, but the results were inconclusive for any known mitochondrial disorders. *See id.* at 33–34. Based on the test results, which showed that [M.S.B.] had elevated blood and urine lactate levels and elevated glutaric acid, Dr. Stein started [M.S.B.] on a cocktail of vitamins for mitochondrial disorders. *See id.* at 34.

Testing of [M.S.B.]'s mitochondrial DNA revealed a G15257A point mutation, which was interpreted as the mildest primary mutation of Leber's hereditary optic

neuropathy (LHON), a condition characterized by degeneration of the optic nerve and progressive vision loss. Pet'r's Ex. 1 at 36. [M.S.B.] was examined by a pediatric ophthalmologist, Dr. Florencio Ching, M.D., who did not report any evidence of the expression of LHON. *Id.* at 38. In October of 1999, [M.S.B.] had a normal cardiac evaluation and the pediatric cardiologist concluded that it was unlikely that [M.S.B.] had a disorder of energy metabolism. *See* Pet'r's Ex. 23 at 114–15. [M.S.B.] was also tested for allergies, and the results showed that she had "moderate" allergies to cow's milk, soybeans, and peanuts. *See* Pet'r's Ex. 1 at 20–25.

Doctor Stein examined [M.S.B.] shortly after her first birthday (a visit which appears to be her last documented appointment with a pediatric neurologist). *See* Pet'r's Ex. 1 at 17–19. At this time, [M.S.B.] was no longer taking "Topamax and all usual anticonvulsant medications" or the mitochondrial cocktail she had been prescribed. *Id.* at 17–18. Instead, she was only taking vitamin B6 and homeopathic medications. *Id.* at 17. Doctor Stein suggested that a mitochondrial disorder might be causing [M.S.B.]'s symptoms and recommended further investigation of this possibility. *Id.* at 18–19. As of May 30, 2000, Dr. DeOrio reported that [M.S.B.] experienced "upwards of 55 seizures per day, along with neuromuscular weakness and poor attention and focusing abilities." Pet'r's Ex. 36 at 24. In December of 2000, at which time [M.S.B.] was twenty-six months old, her occupational therapist determined that she fell into the three- to nine-month age range for various evaluation categories. *See* Pet'r's Ex. 19 at 256. In February of 2002, Dr. DeOrio offered a written opinion that [M.S.B.]'s conjunctivitis in November of 1998 had been a reaction to her first hepatitis B vaccine.[4] *See* Pet'r's Ex. 36 at 31. He relied, in part, on previous test results which showed extremely elevated liver enzymes --- a possible indication of hepatitis. *See id.*

In May of 2003, when [M.S.B.] was four and one-half years old, she underwent an endocrinology evaluation for precocious puberty. *See* Pet'r's Ex. 41 at 44–47. The endocrinologist found "no other chronic conditions other than the seizure disorder," *id.* at 44, noting that it was "not uncommon for children with seizure disorders or central nervous system lesions to present with early pubertal changes," *id.* at 46. At an evaluation more than one year later in July, 2004, a previous chemistry panel was noted to have been "unremarkable," and [M.S.B.]'s liver enzymes were specifically mentioned. *Id.* at 25. It was also noted at that time that [M.S.B.] had a medical history "significant for a seizure disorder and an as yet uncharacterized autoimmune disorder." *Id.* at 24. No medical records appear to have been filed which diagnose [M.S.B.] with an autoimmune condition.

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[4] Doctor DeOrio attributed [M.S.B.]'s "brain damage" to "the Thimerosal in the vaccines she received." Pet'r's Ex. 36 at 31.

[M.S.B.] continues to have daily seizures, and there is no record that she has taken any medications to control her seizures since she was one year old. *See* Pet'r's Ex. 55 at 5, 34; Pet'r's Ex. 1 at 17–19 (evaluation by Dr. Stein in 1999 indicating that [M.S.B.] had stopped taking anticonvulsant medications). Nothing in the record suggests that [M.S.B.] has been evaluated by a neurologist since her seizure medication was discontinued. In July of 2006, Dr. DeOrio summarized [M.S.B.]'s medical condition as "a severe seizure disorder resulting from a hepatitis B vaccine given at three months of age," and also indicated that [M.S.B.] experienced heavy metal poisoning from the mercury preservative Thimerosal.[5] Pet'r's Ex. 45 at 324. [M.S.B.] is wheelchair-bound and remains significantly developmentally delayed, although the magnitude of the delay has not been formally evaluated. *See* Pet'r's Ex. 55 at 31–32.

B. The Petition and Hearing Before the Chief Special Master

[M.S.B.]'s mother filed a petition for compensation on [M.S.B.]'s behalf under the National Vaccine Injury Compensation Program on October 1, 2001, claiming that the administration of [M.S.B.]'s hepatitis B vaccine on October 23, 1998, caused [M.S.B.] to suffer from seizures, encephalopathy, and liver damage. Pet. at 1–2. Petitioner subsequently filed medical records from [M.S.B.]'s treating physicians and hospital visits. *See* Pet'r's Exs. 1–45, 50, 53–58, 93–94. Pursuant to Vaccine Rule 4(c) of the Rules of the United States Court of Federal Claims (RCFC), the Secretary of Health and Human Services (respondent) filed a report on the petition for vaccine compensation, arguing that petitioner failed to demonstrate by a preponderance of the evidence that [M.S.B.]'s vaccinations caused her health problems. Resp't's Rule 4(c) Resp. at 10–11. The Secretary contended that petitioner failed to put forth a reputable medical or scientific theory persuasively connecting the vaccinations to the injury, and noted that the medical records filed by petitioner did not contain any significant opinions regarding the cause of [M.S.B.]'s injuries. *See id.* The report also posited that petitioner failed to show a logical sequence of cause and effect between the vaccine and the injury. *See id.*

Following the filing of respondent's report, petitioner filed expert reports from Dr. Richard Frye, a pediatric neurologist; Dr. Mark Geier, an obstetrician with a doctoral degree in genetics; and Dr. Joseph Bellanti, an immunologist. *See* Pet'r's Exs. 51 (Frye), 59 (Frye, Supplemental Report), 46 (Bellanti), 48 (Geier). At the hearing before the Chief Special Master, and in her post-hearing arguments, petitioner relied solely on Dr. Frye's opinion and the medical literature filed in

[5] Petitioner did not rely upon Dr. DeOrio's offered opinion regarding heavy metal toxicity at the hearing or in post-hearing briefing. *Bast*, 2012 WL 6858040, at *17.

support thereof; for this reason, the Chief Special Master focused on the opinion offered by Dr. Frye in her decision. *See Bast*, 2012 WL 6858040, at *2.[6]

Doctor Frye received his M.D. and a Ph.D. in physiology and biophysics from Georgetown University. Pet'r's Ex. 52. He is board certified in general pediatrics and in neurology, with a special competence in child neurology. *Id.* In his original expert report, Dr. Frye offered two theories of causation: that vaccines can induce autoimmunity; and that vaccines can induce or exacerbate mitochondrial dysfunction in individuals with mitochondrial disorders by increasing oxidative stress. Pet'r's Ex. 51 at 3–6. Incorporated in the second theory was Dr. Frye's belief that "genetic studies have identified a mutation in the SCNA1 sodium channel gene" of [M.S.B.]. *Id.* at 3. He explained that this mutation was associated with "vaccine associated encephalopathy with refractory seizures and intellectual impairment." *Id.* Doctor Frye concluded that in [M.S.B.]'s case, "it is clear that both an environmental (i.e., vaccine) and metabolic factor (i.e., mitochondrial dysfunction), interacted with the SCNA1 mutation to unmask a severe refractory epilepsy." *Id.* at 6. Subsequently, after it came to Dr. Frye's attention that there was no evidence that [M.S.B.] had the SCNA1 mutation or had ever been tested for it, Dr. Frye submitted a supplemental expert report in which the references to this mutation were removed. *See* Pet'r's Ex. 59; *Bast*, 2012 WL 6858040, at *2 n.7. Otherwise, Doctor Frye's report was unchanged. *See* Pet'r's Exs. 51, 59.

Under his first theory, Dr. Frye posits that vaccine-induced autoimmunity and over-activation of the immune system can cause the types of symptoms that [M.S.B.] experienced, and may be related to several neurological disorders. *See* Pet'r's Ex. 59 at 3–4. Doctor Frye's second theory of causation is that [M.S.B.] had an underlying mitochondrial disorder,[7] which made it difficult for her mitochondria to handle reactive oxygen species (ROS), and which ultimately caused her seizures and neurological damage. *See id.* at 4–6. According to Dr. Frye's theory, if mitochondria are not functioning properly, they may not be able to properly process oxidants, leading to an excess of ROS within the cell. *Id.* If this occurs, the oxidative stress caused by the ROS can lead to metabolic decompensation and a neurodegenerative event, such as the seizures and developmental delays suffered by

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[6] The Chief Special Master noted that Dr. Geier's license to practice medicine in Maryland has been suspended due to requirements of public health, safety, and welfare, and that six other states subsequently suspended his license to practice medicine pending the outcome of the Maryland disciplinary proceeding. *Bast*, 2012 WL 6858040, at *1 n.5.

[7] Mitochondria are organelles within cells that produce energy; if they do not function properly, various organs in the body may be adversely affected. *See* Resp't's Ex. A at 4; Resp't's Ex. C at 2; Tr. of Oral Arg. Before Sp. Mstr. (Dec. 6, 2010) at 18.

[M.S.B.]. *Id.* Doctor Frye contends that [M.S.B.]'s December 4, 1998 vaccinations activated her immune system and caused an increase in oxidative stress --- to which she was particularly susceptible due to having a mitochondrial disorder --- and ultimately caused the damage that led to both her seizures and her other neurodevelopmental disorders. *Id.*

In response, respondent filed two expert reports of her own: from Dr. Gerald Raymond, an M.D. and expert in pediatric neurology and neurogenetics; and Dr. Dean Jones, a Ph.D. and expert in mitochondrial oxidative stress. *See* Resp't's Exs. A–D. Respondent also filed medical literature in support of her position. *See* Resp't's Exs. E–H. Doctor Raymond received his M.D. from the University of Connecticut, and served a residency in pediatrics at Johns Hopkins Hospital and a residency in neurology at Massachusetts General Hospital. Resp't's Ex. B. He is currently a professor of neurology at Johns Hopkins University and is board certified in pediatrics, clinical genetics, and neurology, with a special qualification in child neurology. Resp't's Ex. B. Doctor Jones received a Ph.D. in biochemistry from Oregon Health Sciences University, and is currently a professor in the Department of Biochemistry at Emory University School of Medicine. Resp't's Ex. D. Doctor Jones has published between 150 and 200 papers on oxidative stress and has conducted numerous lectures on this topic. *See id.*; Tr. of Oral Arg. Before Sp. Mstr. (Dec. 6, 2010) (Sp. Mstr. Tr.) at 207–08.

Doctor Raymond's report discusses the fact that [M.S.B.] appears to have the mitochondrial point-mutation associated with LHON, but emphasizes that [M.S.B.] has neither manifested symptoms of LHON, nor been shown to have any other mitochondrial defect which might lead to the chain of events described by Dr. Frye. *See* Resp't's Ex. A. Although he notes that the diagnostic criteria for mitochondrial disorders are quite broad and the possibility that [M.S.B.] has a mitochondrial disorder "cannot be excluded," Dr. Raymond explains that a mitochondrial disorder has "not been substantiated as a cause of her epileptic syndrome." *Id.* at 6. Doctor Raymond indicates that [M.S.B.] would be listed in the "possible to probable range" for a mitochondrial disorder, but then goes on to explain that "nearly any individual with a neurologic condition would be so listed." *Id.* In his report, Dr. Raymond also discusses the literature relied upon by Dr. Frye and rejects both of Dr. Frye's proposed theories of causation. *See id.* at 6–7. With respect to the autoimmunity theory, Dr. Raymond explains that Dr. Frye did not identify any medical "literature that demonstrates autoantibodies to any portion of the mitochondria as a result of immunization." *Id.* at 6. Doctor Raymond also rejects Dr. Frye's contention that oxidative stress could have caused [M.S.B.]'s medical problems, stating that "there is no clinical evidence that vaccines may affect individuals with mitochondrial disease" in the manner proposed by Dr. Frye, and that even if this were possible, [M.S.B.]'s upper respiratory infection would be "the more suitable trigger" for the injury. *See id.* at 7.

Respondent's other expert, Dr. Jones, submitted a report which also criticizes Dr. Frye's theories of causation. *See* Resp't's Ex. C. Doctor Jones's report primarily focuses on Dr. Frye's theory of oxidative stress, rejecting that theory as "not sound," and as reflecting "some degree of obfuscation." *See id.* at 4. Doctor Jones explains that oxidants are essential for normal cell signaling, and opines that the scientific evidence does not support the proposition that vaccines can stimulate enough oxidation to cause the symptoms that [M.S.B.] experienced in the time frame in which her symptoms occurred. *See id.* at 4–5. Doctor Jones is also critical of the literature relied upon by Dr. Frye, noting that many of the studies are about responses to infections, which are "not equivalent" to those following vaccinations. *See id.* With respect to Dr. Frye's autoimmune theory, Dr. Jones rejects the theory as "not supported by evidence that [M.S.B.] had symptoms or laboratory tests consistent with an autoimmune response activated by vaccination." *Id.* at 5.

On December 6, 2010, the Chief Special Master held a hearing in this matter. Doctor Frye, testifying for petitioner, was accepted as an expert in child neurology and pediatrics. Sp. Mstr. Tr. at 11. At the hearing, he focused on oxidative stress as the causation mechanism, indicating that his theory of causation does not depend on the autoimmunity theory. *See* Sp. Mstr. Tr. at 109.[8] Doctor Frye provided detailed testimony regarding the petitioner's theory of oxidative stress, and stated that, in his expert opinion, and to a reasonable medical probability, the vaccines that [M.S.B.] received caused her injuries. *See id.* at 12–22. Explaining the oxidative stress theory, Dr. Frye posited that vaccines can cause an increase in oxidative stress, which can damage the mitochondria --- particularly when the mitochondria contain a mutation affecting the electron transport chain --- and that this can cause an excess of ROS, which in turn, causes more damage to the mitochondria. *See id.* at 13. As Dr. Frye explains it, "the vaccine would activate immune processes, which through cytokine and other processes would increase reactive oxygen species." *Id.* at 49. His theory is that this "vicious cycle" can lead to metabolic decompensation and a neurodegenerative event. *See id.* Dr. Frye also discussed three potential "pathways" through which this chain of events could occur. *Id.* at 52–60.[9]

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[8] The autoimmune theory was also not discussed in petitioner's post-hearing brief. *See* Pet'r's Post-Hr'g Br. Although Dr. DeOrio, a family practitioner with no apparent expertise in immunology, made conclusory statements that [M.S.B.] has an autoimmune disorder, the basis for this contention is unexplained. *See* Pet'r's Ex. 36 at 27; Pet'r's Ex. 45 at 324. Moreover, Dr. Bellanti, petitioner's expert immunologist, refrained from concluding that [M.S.B.] had an autoimmune condition. *See* Pet'r's Ex. 46 at 10.

[9] These "pathways" were an immune response in the brain to excess ROS, a mitochondrial dysfunction in which enough energy is not produced to support the brain, and the diversion of antioxidants from the brain to compensate for the reactive oxygen species. *See* Sp. Mstr. Tr. at 59–60.

During the hearing, Dr. Frye provided an overview of the medical literature upon which he relies in support of his theory of oxidative stress. *See* Sp. Mstr. Tr. at 24–43. He also explained in detail the basis for his opinion that [M.S.B.] has a mitochondrial disorder, discussing the diagnostic criteria for mitochondrial disorders set forth in an article co-authored by Dr. F.P. Bernier. *Id.* at 31–34; *see also* Pet'r's Ex. 63 (F.P. Bernier et al., *Diagnostic Criteria for Respiratory Chain Disorders in Adults and Children*, 59 Neurology 1406 (2002)) (Bernier). Specifically, Dr. Frye opined that under that article's classification system, [M.S.B.] has a "probable" mitochondrial disorder because she meets at least one of the "major" criteria of the article --- the clinical criterion requiring an unexplained combination of multi-systemic symptoms in at least three organ systems (in [M.S.B.]'s case, the neurologic, hepatic, and endocrine systems) --- and two of the "minor" criteria, the molecular and the metabolic. *See* Sp. Mstr. Tr. at 33–34; Pet'r's Ex. 63 at 2.[10] Doctor Frye identified [M.S.B.]'s mitochondrial DNA mutation and her exhibition of metabolic indicators of impaired respiratory chain function (in the form of lactate elevation) as fulfilling two of the minor criteria. *See* Sp. Mstr. Tr. at 33–34. In addition, Dr. Frye discussed the timing of the onset of [M.S.B.]'s symptoms and explained that, in his opinion, the timing of her symptoms is consistent with the expected timing under his theory of causation and the medical literature filed in support thereof --- two to four weeks from the date of vaccination. *Id.* at 71.

On cross-examination, Dr. Frye was questioned at length about the literature upon which he relied in forming his opinion regarding the cause of [M.S.B.]'s medical problems. *See, e.g.*, Sp. Mstr. Tr. at 60–78. The respondent also challenged Dr. Frye's focus on the vaccines that [M.S.B.] received as the cause of her injuries, rather than her subsequent upper respiratory infection. *See id.* at 117–18. In

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[10] Under the Bernier criteria, one is defined as having a "probable" mitochondrial disorder when "either one major plus one minor criterion or at least three minor criteria" are met. Pet'r's Ex. 63 at 2. In [M.S.B.]'s case, Dr. Frye contends that one major criterion and two minor criteria are met. The majority of the discussion by the experts and the Chief Special Master focused on one of the major criteria --- a clinical mitochondrial cytopathy --- and its three conditions. The three conditions, which petitioner contends [M.S.B.] meets, are: (1) an unexplained combination of multi-systemic symptoms involving at least three organ systems; (2) a progressive clinical course with episodes of exacerbation; and (3) that other possible metabolic or nonmetabolic disorders have been excluded by appropriate testing. *See id.*; Sp. Mstr. Tr. at 31–34.

response, Dr. Frye stated that he thought that the "multiple vaccines that she received probably caused more activation to the immune system than a . . . mild viral infection would have." *Id.* at 118. The Chief Special Master inquired as to Dr. Frye's assessment that [M.S.B.] experienced a developmental "regression," eliciting the explanation that he used the term "regression" to include the mere failure to acquire additional skills, rather than its customary meaning that previously acquired skills were lost.[11] *See id.* at 121–22.

Doctors Raymond and Jones testified as expert witnesses for respondent, with the former found to be qualified as an expert in neurology and genetics and the latter found to be qualified as an expert in the field of oxidative stress. Sp. Mstr. Tr. at 130, 208. Doctor Raymond testified that, in his opinion, [M.S.B.]'s December 4, 1998 vaccinations did not cause her current neurologic condition. *Id.* at 131. Instead, it was his opinion that [M.S.B.] has an epileptic syndrome, and that "there is very limited evidence that she has a mitochondrial disorder" --- something about which he "would not be overly concerned" were he [M.S.B.]'s treating physician. *See id.* He opined that there was "limited evidence of multisystem disorder" and "really no evidence" of episodes of regression, despite Dr. Frye's testimony to the contrary. *See id.* Noting that [M.S.B.] does have the mutation associated with LHON, but not LHON itself, Dr. Raymond reiterated that he is "not convinced that we have enough evidence that she has a mitochondrial disorder." *See id.* at 131–32.

In explaining his opinion that there was insufficient evidence to conclude that [M.S.B.] has a mitochondrial disorder, Dr. Raymond discussed the Bernier criteria and how [M.S.B.]'s symptoms fit within that framework. *See id.* at 134–152. Doctor Raymond indicated that he would look for more consistently abnormal lab readings, in contrast to [M.S.B.]'s lab results, which he considered to be fairly normal, with a few elevations. *See id.* at 134. For example, Dr. Raymond testified that testing performed in January of 1999 revealed lactate levels on the "high end of normal," a pyruvate level that was normal, a normal amino acid profile, an "essentially" normal cerebral spinal fluid examination, normal aldolase, normal ketones in [M.S.B.]'s blood, and normal levels of the enzymes alanine aminotransferase (ALT) and aspartate aminotransferase (AST). *See id.* at 135–38. Testing in February of 1999 indicated abnormal liver functioning, but Dr. Raymond testified that the anticonvulsants that [M.S.B.] was taking are known to "rev up the liver function system," the result of which would be an elevated liver function test. *See id.* at 139.

During his testimony, Dr. Raymond also called into question whether [M.S.B.] had the type of multi-systemic symptoms contemplated by the Bernier article. *See id.* at 145. While he did not dispute that [M.S.B.] had neurologic

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[11] Doctor Frye stated in his expert report that [M.S.B.]'s case is similar to another case "in which immunizations triggered developmental regression, brain injury and the subsequent development of a seizure disorder." Pet'r's Ex. 59 at 6.

symptoms, Dr. Raymond noted that he did not think that she had hepatic or endocrine abnormalities that would be typical of a mitochondrial disorder, and that with respect to her gastrointestinal system, constipation was "so common in children with intellectual disabilities" that he would hesitate to consider that a sign of a multisystem abnormality. *See id.* at 145, 147. Doctor Raymond also indicated that the Bernier criteria are meant to help determine which patients are appropriate candidates to be tested for mitochondrial disorders via muscle biopsies, and that he thinks that the authors were "trying to lower the criteria" to expand the use of these biopsies. *See id.* at 146. Moreover, Dr. Raymond disputed that [M.S.B.] had the type of "progressive clinical course with episodes of exacerbation" contemplated by the article, *see id.* at 147, noting that, by definition, a seizure disorder involves periods of exacerbation, *see id.* at 150. Instead, he contended that the criteria encompassed mitochondrial disease that was progressive in nature, although allowing for periods of recovery. *See id.* at 150–51. The fact that other possible disorders had not been excluded through appropriate testing, despite substantial developments in the ability to do so in recent years, was also mentioned by Dr. Raymond as a reason the Bernier criteria were not met in [M.S.B.]'s case. *See id.* at 151. He later added that [M.S.B.] also had "unremarkable" MRIs, which he would not have expected if she were suffering from neurodegeneration. *See id.* at 167–68.

On cross-examination, Dr. Raymond was asked about [M.S.B.]'s 2008 alanine to lysine ratio of 3.4, which Dr. Raymond conceded was significantly outside the expected range of 1.5 to 2.5. *See* Sp. Mstr. Tr. at 174. Doctor Raymond indicated, however, that the test did not involve a fasting sample, which could have skewed the results. *See id.* He was also asked about [M.S.B.]'s 2008 lactate level of 87.5, which was well above the expected upper-limit of 19.8. *See id.* at 174–75; Pet'r's Ex. 50 at 18. Doctor Raymond responded that he believed that the lactate level was artificially high, likely due to the mishandling of the sample, *see* Sp. Mstr. Tr. at 175–76, and that he did not think that this "outrageous lactate" level "would actually be consistent with anyone's condition," *id.* at 180, 192. Petitioner's counsel also asked Dr. Raymond to apply to [M.S.B.]'s case the criteria for diagnosing mitochondrial disease advanced in an article co-authored by Dr. E. Morava, which was included among respondent's exhibits. *See id.* at 176–81; Resp't's Ex. H (E. Morava et al., *Mitochondrial Disease Criteria: Diagnostic Applications in Children*, 67 Neurology 1823 (2006)). Using the point system from the Morava article, Dr. Raymond acknowledged that [M.S.B.] could have totaled as many as six points, putting her in the probable (five to seven) range for a mitochondrial disorder. Sp. Mstr. Tr. at 180. He elaborated, however, that he would want to confirm [M.S.B.]'s lab results, particularly the elevated lactate level. *Id.*

Doctor Raymond later clarified on re-direct examination that if he were [M.S.B.]'s treating physician he would not have assigned her a score within the probable range without retesting her lactate level. See *id.* at 192–94. He

emphasized that at the time when one would have expected [M.S.B.]'s alleged mitochondrial disease to be "in full force," there was "very limited" evidence of any sort of dysfunction concerning her electron transport chain. *Id.* at 194. Doctor Raymond would not have assigned a point for gastrointestinal tract disease, reducing the maximum point score to five (including two based on the dubious lactate measurement). *Id*. at 193.

Doctor Raymond also discussed Dr. Frye's characterization of [M.S.B.]'s genetic mutation associated with LHON, explaining that no evidence links this specific point mutation with seizures. *See id.* at 158–61, 184. He also testified that if it were assumed that [M.S.B.] had a mitochondrial disorder affecting her electron transport chain, her upper respiratory infection would produce a much "more enhanced" response than a vaccine and thus would more likely be the cause of her injuries. *Id.* at 185–86.

Doctor Raymond criticized Dr. Frye's reliance on certain literature as supporting his theory of oxidative stress. One article, whose lead author was Dr. Rahul N. Khurana, *see* Pet'r's Ex. 75,[12] had been described as showing that a vaccine could result in an increase in reactive oxygen species, Sp. Mstr. Tr. at 23. Doctor Raymond believed that this animal model, in which bovine retina were injected into rats "to get a horrendous response," has "absolutely nothing to do with vaccination of children," and that to rest a theory concerning the latter on the study was "just nonsensical." Sp. Mstr. Tr. at 171–72. Another article, co-authored by Dr. Joseph L. Edmonds, *see* Pet'r's Ex. 79,[13] was cited as demonstrating that infections are associated with the neurodegenerative episodes in children with mitochondrial disorders. Sp. Mstr. Tr. at 38, 65. Doctor Raymond noted that [M.S.B.]'s point mutation was not among the disorders identified; that the article did not establish causality; and that it discusses infections, rather than vaccines. *See id.* at 187–90, 195. He did acknowledge that "there's nothing that excludes the possibility that" a combination of infection and vaccination could "bring mitochondrial dysfunction to a clinical level," *id.* at 191, but emphasized that none of the literature discusses such a "synergistic event," *id*. at 195. And when asked about two case reports cited by Dr. Frye, *see* Pet'r's Exs. 67 & 68, Dr. Raymond emphasized that in contrast to the patients discussed in the reports, there was no evidence that [M.S.B.] experienced a fever at the time that her seizures first presented, Sp. Mstr. Tr. at 198–200.

Respondent's second expert, Dr. Jones, an expert in the field of oxidative stress, testified that he did not think that Dr. Frye's theory of oxidative stress was

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[12] R.N. Khurana et al., *Mitochodria Oxidative DNA Damage in Experimental Automimmune Uveitis*, 49 Investigative Ophthalmology & Visual Sci. 3299 (2008).

[13] J.L. Edmonds et al., *The Otolaryngological Manifestations of Mitochondrial Disease and the Risk of Neurodegeneration with Infection*, 128 Archives Otolaryngology Head & Neck Surgery 355 (2002).

reliable, as research in the last decade has changed how oxidants are understood to affect the body. *Id.* at 208–09. According to Dr. Jones, the old concept was one of "imbalance" --- if antioxidants did not balance out the oxidants in the body, oxidative stress would result, with a deleterious effect on the body. *See id.* at 209–14. Doctor Jones explained, however, that recent research has shown that this theory is incorrect, as enzymes purposefully generate oxidants because the latter are necessary for normal cell signaling. *See id.* at 214–17. Moreover, Dr. Jones notes that there is no evidence that an excess of oxidants is actually harmful, as Dr. Frye's theory contends, although in certain other contexts, oxidative stress may have an impact on health.[14] *See id.* at 216–22. For example, Dr. Jones explained that oxidants seem to contribute to aging, although the time frame for those effects would be different by orders of magnitude from the time frame proposed by Dr. Frye. *See id.* at 221–22. While Dr. Jones indicated that some things, such as toxic chemicals, can inhibit electron transfer flow in the mitochondria, *see id.* at 255, he reiterated that any oxidants produced though vaccine-induced activation of the immune system would operate as part of the normal cell signaling process, *see id.* at 263.

The difference between how an infection might produce excess oxidants and how a vaccine might do so was also discussed by Dr. Jones, who noted that Dr. Frye's reliance on studies involving infections involved some degree of "obfuscation." *See id.* at 223–25. One reason that the "scientific folklore" of oxidative stress as a central mechanism has persisted, according to Dr. Jones, is because oxidants are difficult to detect and quantify, creating confusion about their impact on disease processes. *See id.* at 224–25. Despite this confusion, Dr. Jones made clear that he does not think that it is possible that oxidants generated at the site of a vaccination could travel to the brain and cause the types of injuries that [M.S.B.] experienced because oxidants are locally metabolized. *Id.* at 227. Moreover, the brain has a rigorous antioxidant system, which, in Dr. Jones's opinion, could not be overcome by oxidants produced as a result of activation of the immune system by a vaccine. *See id.* at 228–29. Instead, Dr. Jones noted that it would require a level of oxygen a thousand-fold greater than that which is present in the body to create enough oxidants to overload the body's antioxidant system and cause an injury, *see id.* at 232–34, and thus he believed that Dr. Frye's proposed causation theory is "not quantitatively reasonable," *id.* at 244.

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[14] Doctor Jones elaborated that while it was clear that an imbalance between oxidants and antioxidants does not itself create oxidative stress or otherwise harm the body, a different type of oxidative stress can affect the body. *See* Sp. Mstr. Tr. at 215–18. He viewed this concept of oxidative stress as a disruption in the signaling pathways, which could be caused by an inhibitor that blocks signaling pathways or by the creation of an abnormal pathway. *See id.*

Doctor Jones also discussed several of the articles relied upon by Dr. Frye, indicating that the articles do not support Dr. Frye's causation mechanism. *See* Sp. Mstr. Tr. at 236–42. In conclusion, Dr. Jones explained that reactive oxygen species play a beneficial role in cell signaling, *id.* at 275, and that he did not think that Dr. Frye's theory of oxidative stress as the cause of [M.S.B.]'s injuries was at all plausible, *id.* at 244.

In her post-hearing brief, petitioner argued that she had met her burden of proof under all three of the *Althen* prongs, and was therefore entitled to relief. Petitioner relied upon Dr. Frye's theory of oxidative stress, and did not discuss the autoimmunity theory. *See* Pet'r's Post-Hr'g Br. Applying the *Althen* factors to [M.S.B.]'s case, petitioner contended that she met the burden of proof by demonstrating that Dr. Frye's theory of oxidative stress causally connects [M.S.B.]'s December 4, 1998 vaccinations with her injuries, by presenting a logical sequence of cause and effect that the vaccinations triggered the underlying mitochondrial dysfunction to cause [M.S.B.]'s injuries, with or without demonstrating a proof of a "rechallenge" event;[15] and by showing a proximate temporal relationship between the vaccination and the onset of [M.S.B.]'s symptoms. *Id.* at 4, 11.

Respondent filed a post-hearing memorandum, arguing that petitioner failed to meet her burden of proof for each of the *Althen* factors. *See* Resp't's Post-Hr'g Mem. With respect to the first prong, respondent argued that Dr. Frye's theory "lacks reliable scientific support" and "is just plain wrong." *Id.* at 8–9. Explaining this position, respondent noted that Dr. Frye's causation theory was based on an imbalance theory of oxidative stress, which "is inconsistent with the current understanding," and therefore, did not meet the reliability standards set forth in *Daubert v. Merrell Dow Pharmaceuticals, Inc.*, 509 U.S. 579 (1993). Resp't's Post-Hr'g Mem. at 10–11. Citing Dr. Jones's hearing testimony, respondent also contended that it is "scientifically implausible" that vaccines could produce enough ROS to overwhelm the body's antioxidant system. *Id.* at 12–14.

With respect to the second prong of *Althen*, respondent argued that petitioner failed to demonstrate by preponderant evidence that [M.S.B.] actually had dysfunctional mitochondria at the time of her vaccination, or at any time thereafter. *See id.* at 14. Respondent noted that no evidence has been presented that the point mutation identified for [M.S.B.] causes seizures; rather, Dr. Frye seemed to reference the fact that [M.S.B.]'s point mutation is in the same protein complex as other point mutations that may do so, and cited this as evidence that [M.S.B.] has dysfunctional mitochondria making her susceptible to epilepsy and neurodevelopmental delays. *See id.* at 15–16. In addition, respondent argued that

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[15] Rechallenge is the occurrence of an adverse event after each administration of the same vaccine in the same individual, without worsened symptoms. See *Capizzano v. Sec'y of Health & Human Servs.*, 440 F.3d 1317, 1322 (Fed. Cir. 2006).

[M.S.B.]'s clinical course was not consistent with mitochondrial dysfunction, and discussed the symptoms which Dr. Frye contended establish that she has a probable mitochondrial disorder. *See id.* at 18–25. Lastly, according to respondent, petitioner failed to provide reliable evidence of a "rechallenge" event, which was raised by petitioner for the first time in her post-hearing brief. *See id.* at 25–27.

Regarding the third *Althen* factor, respondent argued that petitioner failed to meet her burden of proof because the evidence did not support Dr. Frye's proposed timeframe for the onset of symptoms as medically acceptable, and also did not support the contention that [M.S.B.]'s symptoms occurred within the proposed timeframe. *See id.* at 27–30. Challenging Dr. Frye's proposed timeframe, respondent contended that the timeframe "lacks a scientific basis," and according to Dr. Jones, "would be off by [orders] of magnitude." *Id.* at 29. Moreover, respondent noted that [M.S.B.]'s medical records place the onset of her seizures just past the two- to four-week timeframe proposed by Dr. Frye, while the parents' affidavits would place her symptoms "somewhere between 10 days and two weeks after the vaccine," barely within the expected timeframe. *Id.* at 28–29.

In her reply, petitioner disputed respondent's contention that she did not advance a sufficient medical theory connecting the vaccines to [M.S.B.]'s injuries, noting that *Althen's* preponderance standard allows "the finding of causation in a field bereft of complete and direct proof of how vaccines affect the human body." Pet'r's Reply Br. to Resp't's Post-Hr'g Mem. (Pet'r's Reply) at 3 (quoting *Althen*, 418 F.3d at 1280). Petitioner contended that while Dr. Jones has suggested an "alternative approach to oxidative stress," respondent has "offered very little evidence to support her assertion that the scientific and medical communities have completely dismissed the imbalance theory as a viable explanation for oxidative stress." *Id.* at 4. Instead, petitioner argued, the evidence offered by respondent did not demonstrate that Dr. Jones's theory is correct, or that it "has supplanted the imbalance theory." *Id.* Petitioner also addressed respondent's argument that the studies relied upon by Dr. Frye do not support petitioner's theory, *see id.* at 5–7, and noted that two of the articles relied upon by respondent actually use "the oxidant/antioxidant balance theory that Respondent claims is no longer viable," *id.* at 7 (citing Resp't's Exs. T and U).

Petitioner also discussed the second *Althen* factor, and, in particular, the respondent's characterization of Dr. Frye's attempt to explain how [M.S.B.]'s genetic mutation could cause her seizures. *See id.* at 8–9. According to petitioner, Dr. Frye did not claim that [M.S.B.]'s point mutation has been shown to lead directly to epilepsy or neurodegenerative events, but rather testified that "this mutation is in cytochrome b, and other mutations similarly affecting cytochrome b have been shown to cause epilepsy" --- meaning that [M.S.B.]'s mutation may also do so after a vaccine triggers a disruption in mitochondrial function. *Id.* Petitioner contended that she had presented sufficient evidence to show that [M.S.B.]'s mutation did

disrupt her electron transport chain, despite "a lack of definitive experimental proof that [the mutation] causes seizures or neurodevelopmental delay." *Id.* at 9.

Responding to the argument that petitioner failed to prove that [M.S.B.] had the underlying mitochondrial disorder upon which Dr. Frye's theory is predicated, petitioner argued that she had proven by preponderant evidence that [M.S.B.] has such a mitochondrial disorder. *See id.* at 10–13. Petitioner contended that [M.S.B.]'s symptoms fit within the diagnostic criteria for mitochondrial disorders, and disputed various aspects of Dr. Raymond's testimony discussing those criteria. *Id.* Finally, petitioner's discussion of the third *Althen* prong set forth the basis for Dr. Frye's opinion that two to four weeks was a medically appropriate timeframe for the onset of symptoms following [M.S.B.]'s vaccinations, and argued that the onset of [M.S.B.]'s symptoms did, indeed, fall within that timeframe. *See id.* at 13–15.

C. The Chief Special Master's Decision Denying Compensation

In her December 20, 2012 decision, the Chief Special Master determined, based on the preponderance of the evidence and after a thorough review of the record, that [M.S.B.]'s December 4, 1998 vaccinations did not cause her subsequent injuries. *See Bast*, 2012 WL 6858040, at *1. The Chief Special Master found that petitioner failed to meet her burden for each of the *Althen* factors under either the vaccine-induced autoimmunity theory or the mitochondrial dysfunction theory. *See id.* Beginning with a discussion of the credibility of the experts who testified in the case, the Chief Special Master noted that while all of the experts were "unquestionably competent," respondent's experts possessed superior expertise, and their testimony "cogently rebutted petitioner's offered medical theory." *Id.* at *4–5.

In discussing the first *Althen* prong --- whether the petitioner put forth a biologically plausible theory explaining how the vaccines could have caused the sustained injury --- the autoimmunity theory was first considered. Finding no evidence that [M.S.B.] has suffered from an autoimmune condition, other than an unsupported opinion from Dr. DeOrio, the Chief Special Master found that petitioner failed to meet her burden of establishing that [M.S.B.] had the proposed condition upon which the autoimmunity theory rests. *See id.* at *26. The Chief Special Master also noted that Dr. Frye indicated at the hearing that his theory of causation does not depend on the autoimmunity theory. *Id.*

Regarding the mitochondrial dysfunction theory, the Chief Special Master examined Dr. Frye's testimony and concluded that Dr. Frye's understanding of oxidative stress "is not supported by sound and reliable science." *Id.* at *27–28. The Chief Special Master noted that Dr. Frye's theory offers an "older view of oxidative stress" than is currently held by the scientific community, and that Dr. Frye relied upon literature of "questionable relevance." *Id.* at *28. The Chief Special Master explained that Dr. Frye failed to rebut the evidence that oxidants

play a necessary role in normal cell signaling; that the body possesses robust levels of antioxidants which make it very unlikely that reactive oxygen species generated by a vaccine could cause the type of harm alleged; and that the distance between [M.S.B.]'s injection site and the brain make it very unlikely that the briefly-existing reactive oxygen species adversely impacted her brain. *See id.* at *28–33. In discussing the literature relied upon by Dr. Frye, the Chief Special Master found Dr. Frye's extrapolation from the effects of infections to that of vaccinations unpersuasive. *See id.* at *33–34. She also noted that the case studies discussed by Dr. Frye, which involved children with purported mitochondrial disorders, highlight the role of fever in metabolic decompensation --- a symptom which [M.S.B.] notably did not have. *See id.* at *34–38. Thus, the Chief Special Master concluded that petitioner failed to meet her burden under the first *Althen* prong under either of Dr. Frye's theories of causation. *See id.* at *38–39.

The Chief Special Master then discussed the second *Althen* prong, under which petitioner must prove "a logical sequence of cause and effect showing that the vaccination was the reason for the injury." *Id.* at *39–48 (quoting *Althen*, 418 F.3d at 1278). The medical theory offered by Dr. Frye was predicated on the premise that [M.S.B.] actually had dysfunctional mitochondria at the time of her vaccinations --- a premise which the Chief Special Master found petitioner failed to prove by preponderant evidence. *See id.* In reaching this conclusion, the Chief Special Master noted that [M.S.B.]'s point mutation, which is associated with LHON, does not, without more, demonstrate that [M.S.B.] had dysfunctional mitochondria at the time of her vaccination. *Id.* at *39–40. Turning to a discussion of the Bernier criteria, the Chief Special Master evaluated each of the diagnostic criteria relied upon by Dr. Frye and determined that preponderant evidence does not establish that [M.S.B.] meets the criteria for mitochondrial dysfunction. *See id.* at *40–48. Moreover, the Chief Special Master noted that the petitioner downplayed the role of [M.S.B.]'s upper respiratory infection in late December of 1998. *See id.* at *47. By contrast, Dr. Raymond testified that this "clear infectious event" was far more likely to have acted as the trigger pursuant to Dr. Frye's theory than the vaccinations [M.S.B.] received. *See id.* Finally, the Chief Special Master rejected petitioner's rechallenge argument, which was raised for the first time during post-hearing briefing, indicating that petitioner offered little evidence to establish the vaccine-relatedness of [M.S.B.]'s conjunctivitis and upper respiratory infection. *See id.* at *47–48.

Finally, the Chief Special Master found that petitioner failed to meet her burden under the third *Althen* prong, because the latter did not establish by preponderant evidence that [M.S.B.]'s injury occurred within a time frame that is medically appropriate for the alleged causal mechanism. *See id.* at *48–50. In his expert report, Dr. Frye indicated that [M.S.B.]'s symptoms began "approximately 10 days after [her] 2 month vaccinations," apparently relying on the affidavits of [M.S.B.]'s parents. *See id.* at *49 (citing Pet'r's Ex. 59 at 1). At the hearing, Dr.

Frye offered his opinion that the medically appropriate time frame in which one would expect to see symptoms caused by oxidative stress would be two to four weeks. *See id.* The Chief Special Master gave greater credence to [M.S.B.]'s contemporaneously documented medical records, which place the onset of her symptoms narrowly beyond the time frame proposed by Dr. Frye. *See id.* But the Chief Special Master made clear that petitioner failed to meet her burden under prong three of *Althen* for other reasons as well. Specifically, the Chief Special Master rejected the causation mechanism proposed by Dr. Frye, and the articles that he cited as support for his proposed time frame. *See id.* at *49–50. Relying on Dr. Jones's testimony, the Chief Special Master indicated that even if she were to accept Dr. Frye's theory of oxidative stress, the two- to four-week time frame that he proposed is much too short, by decades, to cause the types of injuries alleged. *See id.*

Having determined that petitioner failed to meet her burden under each of the prongs set forth in *Althen*, the Chief Special Master concluded that petitioner was not entitled to compensation.

D. Petitioner's Motion for Review

On January 22, 2013, petitioner filed a motion for review and memorandum of objections pursuant to Vaccine Rules 23 and 24, raising three objections to the Chief Special Master's decision. *See generally* Pet'r's Mot. for Rev. (Pet'r's Mot.). First, petitioner argues that the Chief Special Master's rejection of petitioner's theory of oxidative stress was arbitrary and capricious. *See id.* at 2. Second, petitioner argues that the Chief Special Master's rejection of Dr. Frye's reliance on [M.S.B.]'s parents' affidavits regarding the onset of her symptoms, as well as her "selective reading of the medical record," which precluded a finding of a logical sequence of cause and effect was arbitrary and capricious. *See id.* Finally, petitioner argues that the Chief Special Master's "limitation" of the medically-appropriate temporal association was arbitrary and capricious. *See id.*

The Secretary of Health and Human Services responded to petitioner's motion for review. *See* Resp't's Resp. to Pet'r's Mot. for Rev. (Resp't's Resp.). Respondent contends that the Chief Special Master properly determined that petitioner did not meet her burden under all three *Althen* prongs. *Id.* The Court held oral argument on petitioner's motion. After careful consideration of the medical records, testimony, medical literature in the record, the decision below, and the arguments of counsel, this opinion issues.

II. DISCUSSION

A. Legal Standards

1. The Court's Standard of Review of a Special Master's Decision

Under the Vaccine Act, a special master must award compensation if, "on the record as a whole," she finds "that the petitioner has demonstrated by a preponderance of the evidence" the claims of the petition. 42 U.S.C. § 300aa-13(a)(1)(A) (2012). By this same standard, a special master must find that nothing else is responsible for causing the injury. *Id.* § 300aa-13(a)(1)(B). "The special master or court may not make such a finding based on the claims of a petitioner alone, unsubstantiated by medical records or by medical opinion." *Id.* § 300aa-13(a)(1). A special master must consider all the "relevant medical and scientific evidence contained in the record," including any "diagnosis, conclusion, medical judgment, or autopsy . . . regarding the nature, causation, and aggravation of the petitioner's illness, disability, injury, condition, or death" and "the results of any diagnostic or evaluative test which are contained in the record and the summaries and conclusions." *Id.* § 300aa-13(b)(1). The Act further specifies that "[a]ny such diagnosis, conclusion, judgment, test result, report, or summary shall not be binding on the special master or court." *Id.* A special master is entrusted with evaluating the "weight to be afforded to any" of these sources of information. *Id.* A special master's "assessments of the credibility of the witnesses" are "virtually unchallengeable on appeal." *Lampe v. Sec'y of Health & Human Servs.*, 219 F.3d 1357, 1362 (Fed. Cir. 2000). This deference rests on the special master's "broad discretion in determining credibility because he saw the witnesses and heard the testimony," *Bradley v. Sec'y of Dep't of Health & Human Servs.*, 991 F.2d 1570, 1575 (Fed. Cir. 1993), and extends to assessments of expert testimony. *See Moberly v. Sec'y of Health & Human Servs.*, 592 F.3d 1315, 1325–26 (Fed. Cir. 2010).

Medical records "warrant consideration as trustworthy evidence." *Cucuras v. Sec'y of Dep't of Health & Human Servs.*, 993 F.2d 1525, 1528 (Fed. Cir. 1993). These records are "generally contemporaneous to the medical events," and "accuracy has an extra premium" because a patient's proper treatment is "hanging in the balance." *Id.* Moreover, because medical records are contemporaneous documentary evidence, conflicting oral testimony "deserves little weight." *Id.* (citing *United States v. U.S. Gypsum Co.*, 333 U.S. 364, 396 (1947)).

In reviewing a special master's decision, our court may "set aside any findings of fact or conclusion of law of the special master found to be arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law and issue its own findings of fact and conclusions of law." 42 U.S.C. § 300aa-12(e)(2)(B) (2012). Findings of fact are to be reviewed under the "arbitrary and capricious" standard; legal questions are to be reviewed under the "not in accordance with law"

standard; and an abuse of discretion standard is used for discretionary rulings. *See Munn v. Sec'y of Dep't of Health & Human Servs.*, 970 F.2d 863, 870 n.10 (Fed. Cir. 1992). With respect to the arbitrary and capricious review, "no uniform definition of this standard has emerged," but it is "a highly deferential standard of review" such that "[i]f the special master has considered the relevant evidence of record, drawn plausible inferences and articulated a rational basis for the decision, reversible error will be extremely difficult to demonstrate." *Hines ex rel. Sevier v. Sec'y of Dep't of Health & Human Servs.*, 940 F.2d 1518, 1527–28 (Fed. Cir. 1991).

2. The Standard of Causation in Vaccine Cases

A special master may award compensation through an "off-table" or "causation-in-fact" case. *Pafford v. Sec'y of Health & Human Servs.*, 451 F.3d 1352, 1355 (Fed. Cir. 2006). Causation-in-fact --- the basis for the legal entitlement to compensation when a petitioner's injury is either not listed in the Vaccine Injury Table or did not occur within the time period set forth in the Table --- must be proven under two formulations adopted by the Federal Circuit. *See Pafford*, 451 F.3d at 1355. Petitioners must establish that the vaccine was both a "but-for" cause of the injury and a substantial factor in causing the injury. *See Shyface v. Sec'y of Health & Human Servs.*, 165 F.3d 1344, 1352 (Fed. Cir. 1999). Under a three-part test more recently articulated by the Circuit, petitioners must prove "(1) a medical theory causally connecting the vaccination and the injury; (2) a logical sequence of cause and effect showing that the vaccination was the reason for the injury; and (3) a showing of a proximate temporal relationship between vaccination and injury." *Althen v. Sec'y of Health & Human Servs.*, 418 F.3d 1274, 1278 (Fed. Cir. 2005).[16] Petitioners bear the burden of proving causation by preponderant evidence. *See* 42 U.S.C. § 300aa-13(a)(1)(A).

A petitioner must show more than a proximate temporal relationship between the vaccination and the injury to meet her burden of showing actual causation. *Althen*, 418 F.3d at 1278; *see also Grant v. Sec'y of Dep't of Health & Human Servs.*, 956 F.2d 1144, 1148 (Fed. Cir. 1992). Furthermore, "[t]here may well be a circumstance where it is found that a vaccine *can* cause the injury at issue and where the injury was temporally proximate to the vaccination, but it is illogical to conclude that the injury was actually caused by the vaccine." *Capizzano v. Sec'y of Health & Human Servs.*, 440 F.3d 1317, 1327 (Fed. Cir. 2006). A petitioner could meet the first and third prongs of the *Althen* test without "satisfying the second prong when medical records and medical opinions do not suggest that the vaccine caused the injury, or where the probability of coincidence or another cause prevents the claimant from proving that the vaccine caused the injury by preponderant

[16] Although the Federal Circuit has described the *Althen* test as an "alternative," the very same opinion makes plain that the *Althen* "prongs must cumulatively show" that the *Shyface* standard is met. *See Pafford*, 451 F.3d at 1355.

evidence." *Id*. The sequence only has to be "'logical' and legally probable, not medically or scientifically certain," and thus can be established by "epidemiological evidence and [a] clinical picture," even "without detailed medical and scientific exposition on the biological mechanisms." *Knudsen v. Sec'y of Dep't of Health & Human Servs.*, 35 F.3d 543, 548–49 (Fed. Cir. 1994). Nonetheless, the Federal Circuit has stated that while "epidemiological studies are probative medical evidence relevant to causation," they are not necessarily dispositive. *Grant*, 956 F.2d at 1149.

"The government . . . is permitted to offer evidence to demonstrate the inadequacy of the petitioner's evidence on a requisite element of the petitioner's case[-]in-chief." *de Bazan v. Sec'y of HHS*, 539 F.3d 1347, 1353 (Fed. Cir. 2008). If a petitioner satisfies her burden, she is entitled to compensation "unless the [government] shows, also by a preponderance of evidence, that the injury was in fact caused by factors unrelated to the vaccine." *Althen*, 418 F.3d at 1278 (quoting *Knudsen*, 35 F.3d at 547) (alteration in original).

B. The Chief Special Master's Decision Was Not Arbitrary and Capricious

In her motion for review, petitioner challenges as arbitrary and capricious the determinations of the Chief Special Master regarding each of the three prongs of *Althen*. Pet'r's Mot. at 2, 10–20. Before addressing each specific objection, petitioner's paper contains a prolonged discussion of the evidentiary standard employed in Vaccine Act cases. *See id*. at 4–10. In the course of this discussion, she alleges that the Chief Special Master "misinterpret[ed]" the Act by "requiring 'cause-in-fact,' 'truth,' and/or scientific certainty." *See id.* at 5. The only elaboration of this claim is the general charge (with no citation to the opinion below) that the Chief Special Master engaged in "over-analysis" and "ignored the reasonable reliability of . . . Dr. Frye's theories, the strong temporal relationship [and] the totality of the record and required too much of [M.S.B.]." *Id*. at 8.

Nothing in the Chief Special Master's decision suggests she employed any standard other than the "causation in fact" standard adopted by the Federal Circuit for Vaccine Act cases. *See, e.g.*, *Bast*, 2012 WL 6858040, at *20–23. If, despite the Act's use of the phrase "caused by a vaccine," 42 U.S.C. § 300aa-11(c)(1)(C)(ii)(I)–(II), and the Federal Circuit's frequent use and explanation of the "causation in fact" standard, *see Moberly*, 592 F.3d at 1322, petitioner objects to the Federal Circuit's interpretation of the Act, this criticism should be directed to Congress or the Federal Circuit, and not to our court. In any event, requiring that a medical theory of causation be proven reputable by a preponderance of the evidence is not the same thing as requiring scientific certainty. *See id*.

Petitioner seems to be arguing for a lower standard, under which she prevails as long as her expert claims to have a reliable medical theory of causation,

regardless of any testimony to the contrary by respondent's experts. But the Federal Circuit has made it quite clear that it is the job of our special masters to assess conflicting testimony of expert witnesses in determining whether a reputable theory has been proven. *See Porter v. Sec'y of Health & Human Servs.*, 663 F.3d 1242, 1250–51 (Fed. Cir. 2011) (collecting cases). As we will see, the Chief Special Master well and ably discharged this duty, by a careful and thorough evaluation of the evidence and a rational articulation of her reasoning.

1. The Chief Special Master Properly Found Petitioner's Theory to Be Unreliable

Petitioner contends that she satisfied the first *Althen* prong through Dr. Frye's theory of oxidative stress, and that the Chief Special Master's rejection of this theory of causation was arbitrary and capricious.[17] *See* Pet'r's Mot. at 10–14. To support her argument, she cites another case (now on appeal) in which Dr. Frye advanced the same theory and our court reversed the special master's determination that the theory was unreliable. *See* Pet'r's Mot. at 13–14 (citing *Paluck v. Sec'y of Dep't of Health & Human Servs.*, 104 Fed. Cl. 457 (2012), *appeal docketed*, No. 14-5080 (Fed. Cir. May 1, 2014)). At the hearing, petitioner's counsel identified statements by respondent's experts which purportedly undermine their credibility, and argued that the Chief Special Master should have accordingly discounted their testimony. Counsel also argued that the literature relied upon by respondent's experts was of little relevance to [M.S.B.]'s case because she was already ill on the day of her vaccines and allegedly had dysfunctional mitochondria.

The first prong of *Althen* requires "a medical theory causally connecting the vaccination and the injury" that is based on a "'reputable medical or scientific explanation.'" *Althen*, 418 F.3d at 1278 (quoting *Grant*, 956 F.2d at 1148). It is clear that the standard of proof under the Vaccine Act "is a simple preponderance of evidence; not scientific certainty." *Bunting v. Sec'y of Dep't of Health & Human Servs.*, 931 F.2d 867, 873 (Fed. Cir. 1991). But as the Federal Circuit has explained, under the preponderance standard, "petitioner must do more than demonstrate a 'plausible' or 'possible' causal link between the vaccination and the injury." *W.C. v. Sec'y of Dep't of Health & Human Servs.*, 704 F.3d 1352, 1356 (Fed. Cir. 2013) (citing *Moberly*, 592. F.3d at 1322).

The Court finds that the Chief Special Master did not act arbitrarily and capriciously in rejecting petitioner's theory that oxidative stress resulting from the December 4, 1998 vaccinations caused [M.S.B.]'s injuries. The Chief Special Master based this determination primarily on the testimony of Dr. Jones, a frequently-published expert in oxidative stress. *See Bast*, 2012 WL 6858040, at *4–6, *26–39.

[17] Petitioner does not discuss the rejection of the autoimmunity theory in her motion for review.

She accurately recounted his testimony that an imbalance in reactive oxygen species could not have caused injuries such as [M.S.B.]'s --- including his opinions that the amount of antioxidants available in the human body could not possibly be overwhelmed by the amount of oxidation resulting from a vaccination; that the reactive oxygen species was too short-lived and localized to have harmed [M.S.B.]'s brain; and that the human body's reaction to infection is too different from the reaction to vaccines for studies concerning the former to be used to explain the latter. *Id*. at *29–30, *32–34, *38–39; *see* Sp. Mstr. Tr. at 209–15, 221–22, 224–29, 232–34; Resp't's Ex. C at 2–4. She appropriately noted that much of Dr. Jones's testimony was not rebutted. *Bast*, 2012 WL 6858040, at *33–34. The Chief Special Master also discussed the medical literature upon which Dr. Frye relied and explained why she did not find it to support his theory, crediting the criticisms of respondent's experts. *Id.* at *30–32; *see also* Sp. Mstr. Tr. at 171–72, 230, 236–44. And she discounted the relevance of case reports in which neurodegeneration followed a fever --- a symptom from which [M.S.B.] did not suffer. *Bast*, 2012 WL 6858040, at *34–38.

Based on the foregoing, it is quite clear that the Chief Special Master did not reach her conclusion under prong one of *Althen* in an arbitrary and capricious manner, but instead reviewed the entire record and based her determination on the evidence before her. Petitioner appears to contend that her expert should have been found more persuasive than respondent's experts. *See* Pet'r's Mot. at 13. But, as the Federal Circuit has frequently held, in reviewing Vaccine Act cases courts "do not reweigh the factual evidence, assess whether the special master correctly evaluated the evidence, or examine the probative value of the evidence or the credibility of the witnesses --- these are all matters within the purview of the fact-finder." *Porter*, 663 F.3d at 1249 (citing *Broekelschen v. Sec'y of Health & Human Servs.*, 618 F.3d 1339, 1349 (Fed. Cir. 2010) (citing *Munn*, 970 F.2d at 871)). As long as the record evidence which was relied upon "was not wholly implausible," *Lampe*, 219 F.3d at 1363, the conclusion resting upon it cannot be found arbitrary upon review.

But instead of trying to show the implausibility of the opinions of respondent's expert witnesses, petitioner argues that her expert's opinion was found sufficiently reliable in an unrelated case --- in which neither Dr. Jones nor Dr. Raymond testified. *See* Pet'r's Mot. at 13–14 (citing *Paluck*, 104 Fed. Cl. at 471, 477); *Paluck*, 104 Fed. Cl. at 462 n.4 (identifying respondent's expert witness). Based on the evidence before the court in that case, it was noted that Dr. Frye's theory was "under active, continuing scientific investigation by a range of researchers, showing that it is sufficiently worthy and reliable to merit that extensive scientific inquiry." Pet'r's Mot. at 13 (quoting *Paluck*, 104 Fed. Cl. at 475). But decisions from our court on questions of *law* are merely persuasive authority. *See CBY Design Builders v. United States*, 105 Fed. Cl. 303, 332 n.23 (2012); *Vessels v. Sec'y of Dep't of Health & Human Servs.*, 65 Fed. Cl. 563, 569

(2005). It is hard to see how a decision concerning a question of *fact* could even be persuasive, when there are differences in evidentiary records.[18]

Special masters are "neither bound by their own decisions nor by cases from the Court of Federal Claims, except, of course, in the same case on remand." *Hanlon v. Sec'y of Dep't of Health & Human Servs.*, 40 Fed. Cl. 625, 630 (1998), *aff'd*, 191 F.3d 1344 (Fed. Cir. 1999). As the Federal Circuit has explained: "A special master's acceptance of a theory in one case does not require him or her to accept the theory in subsequent cases involving similar facts or the same vaccine. Rather a different evidentiary record can lead to different outcomes." *Rickett v. Sec'y of Dep't of Health & Human Servs.*, 468 Fed. App'x 952 (Fed. Cir. 2011) (unpublished). Significantly, unlike in the present case, the record in *Paluck* did not include testimony from experts (including an expert in oxidative stress) who credibly rejected Dr. Frye's theory as outdated and not scientifically sound.[19] Here, the Chief Special Master carefully considered the expert testimony, expert reports, and the medical literature filed in support thereof, and concluded that a preponderance of the evidence did not support Dr. Frye's theory. The Court can find no error in this determination.

At the hearing on the motion for review, petitioner's counsel supplemented the grounds covered in the motion with additional arguments, presumably attempting to show the implausibility of respondent's evidence. First, a supposed admission by Dr. Jones was noted, as on cross-examination he was asked if "it's possible that oxidative stress can potentially result in seizures in a system where the cells cannot effectively handle [it]." Sp. Mstr. Tr. at 265. He responded, "I'm really not qualified to answer that question at all." *Id.* According to petitioner, this exchange shows that by Dr. Jones's own admission, he is not qualified to assess the key issue in this case --- whether, as posited by Dr. Frye, oxidative stress could potentially result in the symptoms [M.S.B.] experienced.

Even if the statement could be taken as such an admission, the Court doubts that it could appropriately find a decision to be arbitrary based on one sentence of

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[18] At the hearing before the Court, petitioner suggested that the doctrine of collateral estoppel should bar respondent from challenging a medical theory that was accepted in another case. It has long been recognized, however, that the doctrine of offensive nonmutual collateral estoppel does not extend to the United States government. *See United States v. Mendoza*, 464 U.S. 154, 159–62 (1984).

[19] In *Paluck*, "the only objection to the Palucks' general theory presented by the government's expert was that oxidative stress from vaccines has not been established in humans. . . . Putting aside that objection, then, [the government's expert] otherwise conceded that Dr. Frye's general theory was plausible." 104 Fed. Cl. at 476.

testimony that the petitioner did not even see fit to mention in either of her post-hearing briefs before the Chief Special Master --- much less identify in her motion for review. But in any event, the context shows that Dr. Jones was reluctant to speculate on the causes of seizures. In response to a follow-up question regarding whether oxidative stress could cause seizures by damaging brain cells, Dr. Jones clarified: "As I said, I'm not really qualified to answer that question. I really don't know the causes of seizures and [the likely] causes of seizures." *Id.* This hardly detracts from his testimony in his area of expertise, oxidative stress. As was noted above, Dr. Jones persuasively testified that any reactive oxygen species from a vaccination in the thigh were too few, short-lived and localized to injure the brain, so whether it was possible that oxidative stress in the brain could result in seizures is beside the point. *See id*. at 225–34.

The other statement identified at the hearing is no more availing for petitioner. On cross-examination, Dr. Raymond was asked about a vaccination followed by the type of upper respiratory infection suffered by [M.S.B.]: "And there's nothing that excludes the possibility that when you combine these two small infections they can function to bring mitochondrial dysfunction to a clinical level?" Sp. Mstr. Tr. at 191. Doctor Raymond agreed with the statement. *Id.*[20] Even putting aside the predicate of mitochondrial dysfunction, with which Dr. Raymond disagreed, *see* Sp. Mstr. Tr. at 131–52, not excluding a *possibility* is far from conceding a probability. The preponderance of the evidence standard requires more than proof of a mere possibility. *See Moberly*, 592 F.3d at 1322.

Finally, petitioner's counsel contended that the Chief Special Master arbitrarily failed to discount the articles relied upon by respondent's experts, arguing that [M.S.B.]'s case can be distinguished on the grounds that she was already ill and had dysfunctional mitochondria. But if the medical literature is to be so distinguished or limited, this is a question of fact requiring contrary testimony by petitioner's expert, not just the argument of her counsel. No expert opinion to this effect has been identified. Moreover, under the deferential review standard, a court is not to reweigh the evidence that was before the Chief Special Master and reach its own conclusion as to the viability of Dr. Frye's theory. *See Munn*, 970 F.2d at 871. It is the task of a special master to examine the evidence and determine both its relevance and weight. Our court can only ensure that the Chief Special Master considered all relevant evidence, drew plausible inferences, and articulated a rational basis for her decision. *Hines*, 940 F.2d at 1527. The issue of whether the respondent's studies can be distinguished from [M.S.B.]'s case was one for the Chief Special Master to consider, and it is clear from her detailed discussion of the literature, *see Bast*, 2012 WL 6858040, at *30–38, that she thoroughly examined the evidence of record. All told, her determination that petitioner failed to prove a

[20] Although not mentioned in the motion for review, this statement was included in the post-hearing reply brief before the Chief Special Master. *See* Pet'r's Reply at 14.

reliable theory of causation under the first prong of *Althen* was far from arbitrary. Petitioner's first objection is accordingly rejected.

2. The Chief Special Master Did Not Err in Finding That Petitioner Failed to Prove a Logical Sequence of Cause and Effect

Petitioner also objects to the Chief Special Master's conclusions regarding the second *Althen* prong. Under this prong, a petitioner must establish a "logical sequence of cause and effect showing that the vaccination was the reason for the injury." *Althen*, 418 F.3d at 1278; *Capizzano*, 440 F.3d at 1326 ("'A logical sequence of cause and effect' means what it sounds like – the claimant's theory of cause and effect must be logical."). The petitioner must show "that the vaccine was not only a but-for cause of the injury but also a substantial factor in bringing about the injury." *Althen*, 418 F.3d at 1278 (quoting *Shyface*, 165 F.3d at 1352). While circumstantial evidence may be used to meet petitioner's burden, "[t]here may well be a circumstance where it is found that a vaccine can cause the injury at issue and where the injury was temporally proximate to the vaccination, but it is illogical to conclude that the injury was actually caused by the vaccine" --- for example, "where the probability of coincidence or another cause prevents the claimant from proving that the vaccine caused the injury by preponderant evidence." *Capizzano*, 440 F.3d at 1327.

The Chief Special Master's analysis under the second *Althen* prong centered on the issue of whether [M.S.B.] had an underlying mitochondrial disorder --- the "factual predicate" upon which Dr. Frye's theory of oxidative stress is based. *See Bast*, 2012 WL 6858040, at *39–48. The Chief Special Master first explained that [M.S.B.]'s point mutation, which is associated with LHON, "does not, without more, establish that she had a mitochondrial dysfunction." *Id.* at *39–40. She then discussed the Bernier criteria relied upon by Dr. Frye, concluding that "the constellation of [M.S.B.]'s symptoms do not preponderate in favor of a finding that [M.S.B.] has a mitochondrial disorder, as defined by the Bernier criteria." *Id.* at *40–41. In reaching these conclusions, the Chief Special Master examined the testimony of the expert witnesses, as well as the Bernier article itself and [M.S.B.]'s medical records. *See id.* at *40–46.

The remainder of the Chief Special Master's analysis under the second prong of *Althen* addressed how petitioner "diminished the role of [M.S.B.]'s intercurrent upper respiratory infection" and petitioner's rechallenge argument. *See id.* at *47–48. With respect to the rechallenge argument, which the Chief Special Master noted was raised for the first time in petitioner's post-hearing brief, the Chief Special Master concluded that the argument was "unavailing" because petitioner offered "little more than her own assertions regarding the vaccine-relatedness" of the prior symptoms allegedly part of the rechallenge scenario. *See id.*

In the motion for review, petitioner did not argue that the Chief Special Master was arbitrary in finding that petitioner failed to prove the existence of a mitochondrial disorder. Instead, petitioner first reargued the rechallenge argument from the post-hearing brief. *See* Pet'r's Mot. at 14–16. She then contended that prong two was satisfied by Dr. Frye's testimony alone, on the assumption that prongs one and three have separately been met. *See id.* at 16 (citing *Andreu*, 569 F.3d at 1375; *Capizzano*, 440 F.3d at 1326).

Taking the second argument first, as we have just seen, petitioner did not prove a reliable theory of causation to satisfy the first prong of *Althen*, which is sufficient to doom this argument. Petitioner's points concerning the temporal association of [M.S.B.]'s vaccinations and symptoms will be addressed below under the prong three objection, which the Court also rejects. Moreover, while petitioner is correct that the second *Althen* prong *may* be established through medical opinion testimony alone, the Chief Special Master is not required to blindly rely on such testimony merely because petitioner has offered it. After all, "there is nothing in *Andreu* that mandates that the testimony of a treating physician is sacrosanct – that it must be accepted in its entirely and cannot be rebutted." *Snyder ex rel. Snyder v. Sec'y of Dep't of Health & Human Servs.*, 88 Fed. Cl. 706, 746 n.67 (2009). More fundamentally, in [M.S.B.]'s case, her *treating physicians* did not attribute her condition to an underlying mitochondrial disorder and vaccine-induced oxidative stress.[21] As explained by the Chief Special Master, this theory was only put forward by Dr. Frye, petitioner's expert:

> [M.S.B.]'s treating physicians attributed her health issues variously to congenital brain abnormalities, an evolving seizures disorder that may have been caused by a metabolic disorder, and the effects of [M.S.B.]'s anticonvulsant medications. It is the petitioner's expert, Dr. Frye, who offers *the singular opinion* that [M.S.B.]'s health problems resulted from a vaccine-induced cascade of events—including the development of a seizure disorder—that was facilitated by [M.S.B.]'s mitochondrial point mutation and in turn, produced detrimental levels of excess reactive oxygen species, a condition known as oxidative stress.

Bast, 2012 WL 6858040, at *5 (emphasis added); *see also id.* at *26 n.78.

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[21] The Chief Special Master explains that of [M.S.B.]'s treating physicians, only Dr. Stein indicated that [M.S.B.] might have a mitochondrial disorder. *See Bast*, 2012 WL 6858040, at *46. He initiated treatment for a "possible" mitochondrial disorder because he was uncertain about the cause of [M.S.B.]'s symptoms, and noted that there was little danger in treating her for a mitochondrial disorder, even if it turned out that she did not actually have such a disorder. *See id.* (citing Pet'r's Ex. 23 at 108).

But most importantly, regardless of whether Dr. Frye's testimony alone *could be* sufficient to prove a logical sequence of cause and effect, it is the Chief Special Master who is charged with determining whether his testimony *did* prove this under the second prong of *Althen*. Petitioner has failed to identify any error in the making of this determination.

Turning to her first argument, after explaining how [M.S.B.]'s symptoms purportedly demonstrate a rechallenge scenario, petitioner contends that she "has no burden to present any evidence of specific mechanisms of cause, because the cause and effect are understood to be occurring." *Id.* at 14–16 (citing *Capizzano v. Sec'y of Health & Human Servs.*, No. 00-759V, 2003 U.S. Claims LEXIS 219, at *15 (Fed. Cl. Sp. Mstr. Aug. 5, 2003)). This argument rests on Dr. Frye's testimony that [M.S.B.]'s conjunctivitis following her October 23, 1998 hepatitis B vaccination, and her upper respiratory infection following the December 4, 1998 vaccinations, were "adverse effect[s]" of the vaccinations. *See* Sp. Mstr. Tr. at 17–18, 93–94; Pet'r's Mot. at 14–15. But the Chief Special Master noted that no supportive evidence was filed showing an association between the hepatitis B vaccination and conjunctivitis, *Bast*, 2012 WL 6858040, at *48, and petitioner does not identify any to the contrary. A review of the transcript does not reveal any discussion by Dr. Frye concerning whether the reactions which followed the vaccinations would meet the standards for rechallenge identified by the Institute of Medicine or, indeed, anyone. Given this record, the Chief Special Master accurately concluded that "[p]etitioner has offered little more than her own assertions regarding the vaccine-relatedness of [M.S.B.]'s conjunctivitis and upper respiratory infection," and properly did not "accord much weight to these assertions." *Id.* While a rechallenge event may be strong evidence of causality, petitioner has failed to show that the Chief Special Master's rejection of the rechallenge contention was arbitrary and capricious.

The motion for review ignored the Chief Special Master's critical finding that petitioner failed to prove by preponderant evidence that [M.S.B.] had an underlying mitochondrial disorder at the time of the December 4, 1998 vaccinations. But at the hearing before the Court, petitioner's counsel added an argument challenging the Chief Special Master's reliance on Dr. Raymond's testimony concerning this issue.[22] Petitioner's counsel noted that while being cross-examined about [M.S.B.]'s score under the Morava criteria, *see* Resp't's Ex. H, Dr. Raymond acknowledged that [M.S.B.] could receive a score of six, which would put her in the "probable" range for a mitochondrial disorder.[23] *See* Sp. Mstr. Tr. at 180. Doctor Raymond qualified this

[22] A variation on this argument was included in the post-hearing reply brief below. *See* Pet'r's Reply at 10–13.

[23] Doctor Raymond also explains that the significance of a "probable" score is that it indicates that the patient would be an appropriate candidate for a muscle biopsy, something which was never performed on [M.S.B.]. Sp. Mstr. Tr. at 180.

statement by saying that he would want to see repeat laboratory reports for [M.S.B.]'s lactate levels, which he described as "outrageous." *Id.* On re-direct, Dr. Raymond clarified that he would not assign [M.S.B.] a point for her gastrointestinal symptoms.[24] He further explained that while rigid application of the criteria would assign two points based on the dubious lactate levels, "as a practicing clinician" he would not base a diagnosis on those results but rather would order another test.[25] *Id.* at 192–94.

Doctor Raymond elaborated that when [M.S.B.] originally presented with symptoms, "when the mitochondrial disease should be in full force, we have very limited evidence of a biochemical dysfunction of the electron transport chain . . . Frankly, this is the period of time when I would have thought okay, this is when these would be evident and we're not seeing that." *Id.* at 194. In addition, although Dr. Raymond indicated in his expert report that the possibility that [M.S.B.] has a mitochondrial disorder "cannot be excluded," he explained that "nearly any individual with a neurologic condition would be so listed." Resp't's Ex. A at 6.

A full review of Dr. Raymond's testimony shows that, far from conceding that [M.S.B.] suffered from a mitochondrial disorder, respondent's expert believed to the contrary. He explained why he did not believe that a score in the "probable" range under the Morava criteria was a reliable indicator of her condition. The Chief Special Master fully considered his views in reaching her conclusion on this issue. *See Bast*, 2012 WL 6858040, at *41–46 & nn.117–18. Again, in reviewing these decisions courts "do not reweigh the factual evidence, assess whether the special master correctly evaluated the evidence, or examine the probative value of the evidence or the credibility of the witnesses." *Porter*, 663 F.3d at 1249 (citations omitted). The Chief Special Master undertook a thorough review of the evidence and expert testimony and reasonably concluded that preponderant evidence did not establish that [M.S.B.] had an underlying mitochondrial disorder. This determination was not arbitrary, and petitioner's second objection is rejected.

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[24] Earlier, Dr. Raymond testifed that "chronic constipation is extraordinarily common in children with intellectual disabilities, autism and a variety of other neurologic features. It really doesn't speak to a specific mitochondrial characteristic." Sp. Mstr. Tr. at 177.

[25] As noted, Dr. Raymond testified that the reported lactate levels were so high that he did not think they "would actually be consistent with anyone's condition." Sp. Mstr. Tr. at 192.

3. The Chief Special Master Did Not Err in Her Analysis of Petitioner's Proposed Time Frame for the Onset of Symptoms

Petitioner also objects to the Chief Special Master's analysis of the third *Althen* prong, which requires that petitioners establish "a proximate temporal relationship between vaccination and injury." *Althen*, 418 F.3d at 1278. The Federal Circuit has held that this proximate temporal relationship must occur within a "medically acceptable" timeframe. *See de Bazan*, 539 F.3d at 1352; *Pafford*, 451 F.3d at 1358; *Porter*, 663 F.3d at 1266. The Chief Special Master determined that petitioner did not meet her burden under this prong for two reasons --- petitioner did not sufficiently prove that [M.S.B.]'s symptoms actually occurred within the timeframe proposed, and moreover did not establish that the timeframe was medically acceptable. *Bast*, 2012 WL 6858040, at *48–51.

In her motion for review, petitioner challenges both of these determinations. Petitioner first argues that [M.S.B.]'s parents' affidavits establish that [M.S.B.]'s symptoms occurred within the two- to four-week timeframe proposed by Dr. Frye, and that the Chief Special Master improperly discounted these affidavits. *See* Pet'r's Mot. at 16–19. The Chief Special Master explained in her opinion that the parents' recollections of the timing of [M.S.B.]'s symptoms differ from the timing reflected in [M.S.B.]'s medical records, *see Bast*, 2012 WL 6858040, at *8,[26] and indicated that she would rely upon the contemporaneous medical records to the extent that the affidavit testimony "conflicts with or is unsupported by the medical records," *id.* at *6 (citing *Cucuras v. Sec'y of Health & Human Servs.*, 993 F.2d 1525 (Fed. Cir. 1993)). Petitioner challenges this decision as arbitrary and capricious, contending that the two forms of evidence do not contradict each other, but rather reflect an absence of correlative evidence in the record, making it improper not to afford more weight to the parents' affidavits. *See* Pet'r's Mot. at 16–17 (citing *Murphy v. Sec'y of Health & Human Servs.*, 23 Cl. Ct. 726, 733 (1991), *Campbell ex.*

[26] As the Chief Special Master explained, "[M.S.B.]'s parents asserted that 'within ten days of the vaccine[,]' [M.S.B.] developed a 'pretty bad' upper respiratory infection which required a pediatric visit." *Bast*, 2012 WL 6858040, at *8. Since the vaccinations were administered December 4, the recounted visit would have occurred "on or about December 14, 1998," but [M.S.B.]'s contemporaneous medical records indicate that she saw the pediatrician on December 30, 1998, for cold symptoms present by that time for one week. *Id.* (citing Pet'r's Ex. 23 at 6). [M.S.B.]'s parents also recalled that [M.S.B.] began having "tics" on or about December 21, 1998, and that she was having grand mal seizures by January 4, 1999. *Id.* at *8 n.24 (citing Pet'r's Ex. 23 at 6). The Chief Special Master noted that there were no references to tics or tremors in the records from [M.S.B.]'s December 30, 1998 sick visit, and the records from her January 11, 1999 visit indicated that she had been experiencing stiffening and rhythmic moving of her extremities for about five days. *Id.*

rel. Campbell v. Sec'y of Health & Human Servs., 69 Fed. Cl. 775, 779 (2006), and *Camery v. Sec'y of Health & Human Servs.*, 42 Fed. Cl. 381, 391 (1998)).

While petitioner is correct that an absence of correlative evidence is certainly less significant than the existence of evidence that actually negates a witness's recollection, it is still the task of the Chief Special Master to weigh such evidence and the Court affords much deference to the Chief Special Master's determination. Here, the Chief Special Master carefully examined the evidence before her regarding the timing of the onset of [M.S.B.]'s symptoms. She detailed the extent of the conflicts between the parents' affidavits and the medical records, and noted the diligence of [M.S.B.]'s parents in seeking treatment during this time period. *See, e.g.*, *Bast*, 2012 WL 6858040, at *8. She also made note of the general presumption in favor of contemporaneous medical records over later-recorded recollections.[27] *See id.* at *6. Moreover, the parents' recollection of the onset of upper respiratory infection symptoms *was directly contradicted* by the medical records, as the latter indicate that as of December 30, 1998, [M.S.B.]'s cold symptoms were present for one week --- which would be nineteen days after the vaccinations. *See* Pet'r's Ex. 23 at 6.

The Court can find no error in the Chief Special Master's decision to afford greater weight to the contemporaneous medical records than to the parents' later-recorded recollections, particularly in light of the extensive documentation of [M.S.B.]'s doctor visits when her symptoms first began to appear. But the decision on the timing of the onset of symptoms was of slight significance compared with the Chief Special Master's determination that Dr. Frye's proposed timeframe of two to four weeks is "much too short a period of time for oxidative stress to have caused the degree of injury alleged." *Bast*, 2012 WL 6858040, at *49. This was the primary reason for the finding that petitioner did not meet her burden under the third prong of *Althen*.

Petitioner also challenges this aspect of the Chief Special Master's decision under prong three of *Althen*. Pet'r's Mot. at 18–19. Petitioner's argument boils down to noting that another judge in another case reversed a special master for basing the onset of symptoms under Dr. Frye's oxidative stress theory on "a hard and fast limit of two weeks." *Id.* (quoting *Paluck*, 104 Fed. Cl. at 482). The relevance of this eludes the Court. The Chief Special Master relied on the

[27] In *Campbell*, a special master's decision not to conduct an evidentiary hearing was found arbitrary and capricious in light of a similar tension between medical records and later recorded recollections. *See Campbell*, 69 Fed. Cl. 775, 779–80 (2006). Here, in contrast, a hearing was held, at which petitioner was present and chose not to testify. *See Bast*, 2012 WL 6858040, at *6.

testimony of Dr. Jones that, even if it were possible for [M.S.B.]'s symptoms to occur as alleged by Dr. Frye, it would take decades, not weeks, for such harm to occur. *See, e.g.*, *Bast*, 2012 WL 6858040, at *50. A decision, based on a different factual record, that it was arbitrary to require that symptoms manifest within fourteen days, hardly shows that the decision under review was reached in an arbitrary manner.

It is clear to the Court that the Chief Special Master properly examined the evidence before her, including the reports and testimony of all of the experts, in reaching her conclusion that Dr. Frye's testimony was not persuasive concerning *Althen* prong three. *See id.* at *28–30, *48–50. Petitioner does not even attempt to identify any errors in the Chief Special Master's understanding of the crucial testimony of Dr. Jones. Instead, petitioner again cites *Paluck*, in which a special master was purported to have based his assessment of Dr. Frye's testimony on matters of style. Pet'r's Mot. at 19 (citing *Paluck*, 104 Fed. Cl. at 475–76 n.26). But nothing of the sort has been identified in the decision under review. The Chief Special Master thoroughly explained her reasons for finding the testimony of respondent's experts to be more persuasive than Dr. Frye's, in general and as pertaining to the prong three analysis. *See, e.g.*, *Bast*, 2012 WL 6858040, at *4–6, *23–25, *48–50. The assessment of the reliability of expert testimony is particularly entrusted to special masters as the finders of fact. *See Porter*, 663 F.3d at 1250–51; *Moberly*, 592 F.3d at 1325–26. The Chief Special Master has "considered the relevant evidence in the record, drawn plausible inferences, and articulated a rational basis for the decision," *Hines*, 940 F.2d at 1528, and the evidence relied upon "was not wholly implausible," *Lampe*, 219 F.3d at 1363. Her determination that petitioner failed to prove a medically-appropriate time frame under the third prong of *Althen* was not arbitrary but instead quite rational. Petitioner's third objection to the decision under review is thus rejected.

III. CONCLUSION

For the reasons stated above, the petitioner's motion for review is **DENIED** and the decision of the Chief Special Master is **SUSTAINED**. The Clerk of Court is directed to enter judgment for respondent.

IT IS SO ORDERED.

s/ Victor J. Wolski

VICTOR J. WOLSKI
Judge